

RECOMMENDATIONS FOR THE EVALUATION AND MANAGEMENT OF NAUSEA AND VOMITING IN EARLY PREGNANCY

INTRODUCTION:

DEFINITIONS

Nausea: An unpleasant feeling in the throat or epigastric region alerting one that vomiting is imminent [1]

Vomiting: The forceful expulsion of gastric contents through the mouth [1]

Hyperemesis Gravidarum: severe nausea and vomiting with onset prior to the 20th week of pregnancy that may lead to weight loss, dehydration, electrolyte disturbances or death [2]

Nausea and Vomiting of Pregnancy: nausea and vomiting during gestation not attributable to any other physiologic cause

EPIDEMIOLOGY:

- At least 66-80% of women experience nausea and 50% emesis in the first trimester [3-4].
- Four million pregnant women in the US are affected annually [5].
- Nausea and vomiting typically lasts 35 days [4].
- Eighty percent of women have nausea that lasts all day [4].
- Nausea and vomiting typically begins during the 4th to 8th week of gestation and lasts through the 14th-16th weeks [3].
- Fifty percent of women have relief by the 14th week of gestation and 90% have relief by week 22 [4].
- Incidence of nausea and vomiting tends to be inversely associated with the woman's age [2].

PATHOPHYSIOLOGY:

- Expected changes with pregnancy
 - The peristaltic activity of the gastrointestinal (GI) system is reduced resulting in hypoactive bowel sounds [3]
 - Smooth muscles relax in the GI tract (atony) and may contribute to nausea and vomiting [3].
- Pathogenesis of unspecified nausea and vomiting.
 - Afferent impulses from the pharynx, gastrointestinal tract, chemoreceptor trigger zone, and the limbic system stimulate the vomiting center (VC) located in the medulla [1-2].
 - Stimulation of the VC center results in transmission of impulses to the salivation center, respiratory center and musculature. Vomiting results from contraction of

the pharyngeal, GI and abdominal musculature [1].

- The precise etiology of NVP remains unclear. There are three prevalent theories
 - Endocrine theory: It has been postulated that elevated levels of progesterone, estrogen and human chorionic gonadotropin (HCG) precipitate nausea and vomiting. Rises in progesterone relax smooth muscle in the gastrointestinal (GI) system thereby contributing to decreased gastric motility and slowed gastric emptying. HCG has a thyroid stimulating affect that may precipitate nausea and vomiting [2-3].
 - Metabolic theory: Vitamin B-6 (pyridoxine) deficiency has been hypothesized as a trigger of nausea and vomiting in pregnancy [2].
 - Psychosomatic theory: Studies suggest that the prolonged duration of nausea and vomiting of pregnancy is associated with social difficulties, especially lack of social support. Increased nausea and vomiting is also associated with higher levels of depression, although the cause-effect relationship is unclear [2].

SUBJECTIVE ASSESSMENT:

HISTORY

- History of progression of this pregnancy
 - Presence of multiple fetuses
 - Prenatal health care
 - Complications
- Diet history, with special attention to current fluid intake
- Current medications
- Past surgical history, particularly abdominal surgeries
- Past Medical History
 - Past gynecological and obstetric history
 - Cholecystitis or GI disorders
 - Thyroid disorders
 - Depression
- Social History
 - Exposure to communicable diseases
 - Environmental exposures
 - Access to prenatal health care
 - Roles, responsibilities, employment
 - Absenteeism
- History of present illness
 - Onset
 - Duration
 - Emesis
 - Color
 - Volume
 - Frequency
 - Quality
 - Precipitating and alleviating factors
 - Any home treatment attempts
- Associated symptoms
 - Belching or flatus

- Diarrhea or constipation
- Abdominal pain
 - Location
 - Severity
 - Quality
 - Radiation
 - Precipitating and alleviating factors
- Other evaluation tools: Rhodes Index of Nausea and Vomiting
 - This eight-question tool assesses the severity and frequency, as well as the distress from nausea and vomiting [6].
 - This tool has been demonstrated to be both valid and reliable in this population [6-7].

FOCUSED REVIEW OF SYSTEMS

- General, constitutional
 - Fatigue
 - Comfort level
 - Chills
- Gastrointestinal
 - Abdominal pain
 - Appetite
 - Associated GI symptoms
- Psychological
 - Interference with daily activities
 - Perceived stress levels
 - Depression
 - Coping skills
- Genitourinary
 - CVA pain
 - Dysuria

OBJECTIVE ASSESSMENT:

FOCUSED PHYSICAL ASSESSMENT

- Vital signs: fever, tachycardia, or postural hypotension
- General appearance
 - Emotionally distressed
 - Toxic appearance
- Weight gain or loss
- Hydration status
 - Skin turgor
 - Dry versus moist mucous membranes
 - Oliguria
- Cardiovascular status
 - Quality of pulse: strong versus thready
 - Tachycardia
 - Postural hypotension

- Abdominal
 - Bowel sounds (hypoactive can be normal in pregnancy)
 - Tenderness, rigidity, guarding, rebound, distention
 - Hepatosplenomegaly
 - Epigastric, Murphy's or McBurney's point tenderness
- Genitourinary
 - CVA tenderness
 - Suprapubic tenderness
- Fetal well being, as appropriate for gestational age
 - Heart tones
 - Fundal height

DIAGNOSTIC PROCEDURES

- Urinalysis to rule out infection and/or dehydration
- Electrolytes if dehydration is suspected or excessive vomiting
- TSH to rule out thyroid disease
- CBC, amylase, lipase, liver profile if infectious or inflammatory cause is suspected
- Imaging if indicated for acute abdominal process
- Quantitative beta hCG if multiple gestation or molar pregnancy suspected

DIAGNOSIS:

- The diagnosis of NVP is one of exclusion
- Differential diagnoses
 - Acute gastroenteritis both viral and bacterial
 - Medication side effects
 - Cholecystitis
 - Appendicitis
 - Obstruction
 - Hepatitis
 - Pancreatitis
 - Thyroid disease
 - Multiple gestation
 - Molar pregnancy
 - Urinary tract infection

NONPHARMACOLOGIC THERAPY:

ALTERATION OF NORMAL ACTIVITIES AND REDUCTION OF ENVIRONMENTAL STIMULATION

A qualitative analysis of 124 diaries provided by pregnant women found that frequent naps or rest periods, especially after meals, reduced the frequency, severity, and duration of nausea and vomiting in pregnancy. The diaries also revealed that a reduction in sensory stimulation such as walking, talking on the phone, loud noises, and tight clothing reduced NVP [8].

The authors state that results of this study cannot be generalized to the entire population of

symptomatic pregnant women, since the sample was not randomly selected and could not be quantified. However, the interventions pose no danger to the mother or fetus and therefore should be offered. (strength of recommendation B; quality of evidence III)

ACUPRESSURE AND ACUPUNCTURE

Acupressure and acupuncture stimulate the body's integrative regulatory systems and activate a variety of endocrine and neurologic mechanisms, which in turn stimulate a variety of physiologic functions toward homeostasis. For nausea and vomiting, manual or wristband acupressure is applied at the P6 "Neiguan" pressure point, on the volar surface of the forearm, about three fingerbreadths from the distal wrist crease and between the two tendons.

A 1994 randomized, blinded study found that acupressure was effective in reducing symptoms of nausea, but not frequency of vomiting, in pregnant women [9]. However, a 1996 study failed to find a medical benefit from the use of P6 acupressure [10]. On the other hand, studies examining the use of wristbands to administer acupressure have shown these to be an effective method to decrease NVP [11-12].

Though the evidence for the therapeutic benefit of manual P6 acupressure is conflicting, the evidence regarding its use through wristbands is consistent. Acupressure is low in cost and is a harmless modality worth offering (strength of recommendation A; quality of evidence I).

Acupuncture uses needles instead of pressure to stimulate points, and is thought to be more effective than acupressure because it provides a stronger stimulus. However, research has failed to substantiate its use [13].

While relatively harmless, acupuncture is more costly than acupressure in that a trained practitioner must be consulted. Due to the lack of research for this modality, acupuncture for the control of nausea and vomiting in early pregnancy cannot be recommended at this time (strength of recommendation E; quality of evidence I).

DIET

In women with first trimester pregnancy, protein meals selectively reduce nausea and gastric slow wave dysrhythmias [14] (strength of recommendation A; quality of evidence II-1).

Other modifications such as frequent small meals and avoiding strong odors may also be helpful [8]. The notion that nausea and vomiting of early pregnancy protects women from "harmful" meats and vegetables has not been substantiated by scientific inquiry [15].

NUTRITIONAL SUPPLEMENTS:

PYRIDOXINE (VITAMIN B6)

Pyridoxine has proven to be effective in reducing NVP. Two randomized clinical trials have been published to date [16-17]. Pyridoxine in doses of 10-25 mg orally every eight hours on an intermittent basis of 2-3 days at a time are recommended as a first-line therapy for NVP

(strength of recommendation A; quality of evidence I).

The use of pyridoxine in the treatment of nausea and vomiting of pregnancy has been studied since the early 1940s [18-20]. Pyridoxine carries pregnancy classification A [21]. The available evidence does not suggest a teratogenic risk.

GINGER

Ginger has been studied in many forms: dried ginger root, ginger tea from fresh ginger root, and *Zingiber officinale* extract. The actual form studied determines what active ingredients are present. The primary active ingredients in ginger are thought to be a class of compounds called the gingerols. 6-Gingerol and 6-shogaol are implicated in ginger's antinauseant properties as they are found to suppress gastric contraction and increase both gastrointestinal motility and spontaneous peristaltic activity [22].

Two randomized clinical trials of ginger in the treatment of nausea and vomiting in pregnancy have demonstrated that ginger is effective over placebo. One trial was a randomized, double blind, crossover study of twenty-seven pregnant women with hyperemesis gravidarum. Subjects were given 250 mg of dried ginger root contained in a capsule four times a day. Ginger was shown to significantly decrease both nausea and vomiting of hyperemesis gravidarum [22]. A recent randomized, double-blind, placebo-controlled clinical trial of seventy pregnant women showed this same preparation and regimen of ginger effectively reduced both nausea and vomiting in pregnant women not categorized as hyperemesis gravidarum. No adverse effects of ginger on pregnancy outcome were detected [24].

Two randomized, controlled, experimental rat studies have been conducted to evaluate the effect of ginger on fetal development [25-26]. Ginger produced neither maternal nor developmental toxicity at daily doses up to 1000 mg/kg of body weight. With doses of 2200 mg/kg and 5500 mg/kg in the Wilkinson study, there was increased embryonic loss without a concentration-related effect and treated fetuses were significantly heavier than controls, perhaps secondary to the increased calories present in the ginger tea. Considering the evidence from these two studies of fetal development in rats, ginger appears to be safe in concentrations less than 1000 mg/kg. The recommended human dose is 500 to 1000 mg/day [23-24] far less than that used in the above rat studies.

Ginger appears to be effective in the reduction of nausea and vomiting in pregnancy without adverse effects on pregnancy outcome (strength of recommendation B; quality of evidence I). The recommended dose is 250 mg four times a day.

PHARMACOLOGIC THERAPY:

If a trial of nonpharmacologic interventions is not successful, or if symptoms are severe, medications should be offered.

Current randomized, double-blind, placebo-controlled trials of antinausea and antiemetic medications given in pregnancy are scarce due to the inherent ethical and medicolegal issues involved in such research. However, it is possible to draw some conclusions based on the

evidence that is available.

DOXYLAMINE:

Several antihistamines have been used to treat NVP. The best studied of these is doxylamine, which carries a pregnancy classification of A (no evidence of risk). Doxylamine is commonly given concurrently with pyridoxine (vitamin B6), which also carries pregnancy classification A. This combination was found in Bendectin, which was voluntarily withdrawn from the market in 1983 following allegations of possible teratogenic effects. Bendectin was originally formulated as a compound of doxylamine, pyridoxine and dicyclomine. In 1976 dicyclomine was removed from the formulation. A meta-analysis of sixteen cohort and eleven case control studies concluded that there is no evidence that the original Bendectin formulation contributes to birth defects [27] (quality of evidence II-2). Another meta-analysis reviewed 12 cohort and three case-control studies of both the two- and three-drug formulation. Again, no increased risk for malformations was detected [28] (quality of evidence II-2).

Studies demonstrate that this combination of medication is efficacious in treating NVP. A meta-analysis of four clinical trials found that a combination of doxylamine/pyridoxine (with and without dicyclomine) was effective [28] (quality of evidence II-2). A review by the Cochrane groups also found that the three-drug combination was effective in reducing nausea [29]. A correlational study described the increase in hospitalizations for excessive vomiting in pregnancy that occurred with the voluntary withdrawal of Bendectin from the Canadian market. The same study demonstrated the decline in hospitalizations when Diclectin (containing doxylamine 10mg and pyridoxine 10 mg) was released in Canada [30] (quality of evidence II-3). The authors of one meta-analysis describe a regimen for the prevention of recurrence of nausea and vomiting in which two Diclectin tablets are taken at bedtime. If symptoms persist one tablet may be added in the morning and another may be added in the afternoon [31]. The safety of Diclectin in doses greater than four tablets per day has also been documented [32] (quality of evidence III). Doxylamine is available over-the-counter in the United States under the brand name Unisom, a 25 mg scored tablet. It is reasonable to recommend that one half of a tablet, in combination with pyridoxine 10 mg be given up to three times a day. The provider should note that the doxylamine insert advises, "Do not take this product if pregnant or nursing a baby," and counsel the patient accordingly. The patient should also be counseled as to the sedating effects of doxylamine. (strength of recommendation A)

OTHER FIRST GENERATION ANTIHISTAMINES:

Other first generation antihistamines (for example, diphenhydramine, pregnancy classification B; dimenhydrinate, pregnancy classification B; hydroxyzine, pregnancy classification C) have favorable safety profiles. One meta-analysis revealed no association between first trimester antihistamine use and major malformations [33] (quality of evidence II-1). Another meta-analysis demonstrated no teratogenic effect [34] (quality of evidence II-2). A third meta-analysis showed no increased risk for anomalies [28] (quality of evidence II-1). Pooled data indicate that antihistamines are effective in treating NVP, however, the data are not homogenous [28] (quality of evidence II-2). Furthermore the meta-analyses do not report dosages. Sedation is a common side effect of first generation antihistamines. (strength of recommendation B)

PHENOTHIAZINES:

A meta-analysis failed to show any teratogenic effect of phenothiazines [28] (quality of evidence II-1). However, one case of fatal shock was reported when a pregnant woman with undiagnosed pheochromocytoma was given promethazine [34] (quality of evidence III). Phenothiazine effectiveness was demonstrated in a meta-analysis of three randomized control trials [28] (quality of evidence I). Promethazine (pregnancy classification C) is available both as an oral preparation and as a rectal suppository. Sedation is a common side effect. (Strength of recommendation B)

FOLLOW UP:

The patient should be counseled on signs of dehydration including dry skin, dry mucosa, decreased voids and concentrated urine. The patient should return for follow up in 2-4 weeks, or sooner if she notes signs of dehydration, increased nausea or persistent vomiting. Follow up evaluation includes assessment of weight gain, quality of life, hydration status, Rhodes score and absenteeism from work.

REFERRAL:

If the condition progresses to hyperemesis gravidarum the patient will likely require inpatient management.

The algorithm for "Recommendations for the Evaluation and Management of Nausea and Vomiting in Early Pregnancy" is available on request from the guideline developer.

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Rhodes Index of Nausea and Vomiting

During the past 12 hours, have you vomited or thrown up...

☐ 7 or more times ☐ 5-6 times ☐ 3-4 times ☐ 1-2 times ☐ 0 times

During the past 12 hours, how much distress have you felt from retching or dry heaves?

☐ no distress ☐ mild distress ☐ moderate distress ☐ great distress ☐ severe distress

During the past 12 hours, how much distress have you felt from vomiting or throwing up?

☐ severe distress ☐ great distress ☐ moderate distress ☐ mild distress ☐ no distress

During the past 12 hours, for how long have you felt nauseated or sick at your stomach?

☐ none ☐ 1 hr or less ☐ 2-3 hr ☐ 4-6 hr ☐ more than 6 hr

During the past 12 hours, how much distress have you felt from nausea or sickness at you stomach?

☐ no distress ☐ mild distress ☐ moderate distress ☐ great distress ☐ severe distress

During the past 12 hours, how much did you vomit or throw up each time that you vomited or threw up?

☐ very large amount (3 or more cups) ☐ large amount (2-3 cups) ☐ moderate amount (half to 2 cups)
☐ small amount (up to half a cup) ☐ none

During the past 12 hours, how many separate or different times have you felt nauseous or sick to your stomach?

☐ 7 or more times ☐ 5-6 times ☐ 3-4 times ☐ 1-2 times ☐ 0 times

During the past 12 hours, how many times have you had retching or dry heaves without bringing anything up?

☐ no periods ☐ 1-2 periods ☐ 3-4 periods ☐ 5-6 periods ☐ 7 or more periods